

What is Claimed:

1. A method of inhibiting release of CD40 ligand, thromboxanes, or prostaglandin E2, or inhibiting CD40 ligand surface expression, by mammalian
5 platelets, the method comprising:
contacting mammalian platelets with an effective amount of PPAR γ , a PPAR γ agonist, an RXR agonist, or a combination thereof, whereby said contacting inhibits release of CD40 ligand, thromboxanes, prostaglandin E2, or a combination thereof, and/or inhibits CD40 ligand surface expression by the mammalian platelets.
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2. The method according to claim 1 wherein the mammalian platelets are human platelets.
3. The method according to claim 2 wherein the PPAR γ is human
15 PPAR γ .
4. The method according to claim 1 wherein said contacting inhibits release of CD40 ligand by platelets.
- 20 5. The method according to claim 1 wherein said contacting inhibits release of thromboxanes by platelets.
6. The method according to claim 5 wherein the thromboxane is thromboxane B₂.
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7. The method according to claim 1 wherein both the PPAR γ agonist and the RXR agonist contact the mammalian platelet.
8. The method according to claim 1 wherein said contacting
30 inhibits CD40 surface expression by platelets.
9. The method according to claim 1 wherein the PPAR γ agonist is selected from the group consisting of cyclopentenone class prostaglandins, lysophosphatidic acid or its derivatives, thiazolidinediones, glitazones, tyrosine-
35 derived agonists, indole-derived agonists, and combinations thereof.

10. The method according to claim 1 wherein the RXR agonist is 9-*cis*-retinoic acid, *trans*-retinoic acid, synthetic RXR agonists, and combinations thereof.

5 11. The method according to claim 1 wherein the mammalian platelets are *in vitro* or *ex vivo*.

12. The method according to claim 1 wherein the mammalian platelets are *in vivo*.

10 13. The method according to claim 12 further comprising:
administering PPAR γ , the PPAR γ agonist, the RXR agonist, or an inducer of a PPAR γ agonist to a mammal in a manner that provides for said contacting.

15 14. The method according to claim 13 wherein the inducer of a PPAR γ agonist is decorin or fragments thereof, or an enzyme that catalyzes formation of prostaglandin D₂ precursor.

20 15. The method according to claim 13 wherein said administering is carried out via topical application, intranasal instillation, inhalation, intravenous injection, intra-arterial injection, intramuscular injection, application to a wound site, application to a surgical site, intracavitary injection, by suppository, subcutaneously, intradermally, transcutaneously, by nebulization, intraplurally, intraperitoneally,
25 intraventricularly, intra-articularly, intra-aurally, intraocularly, or intraspinally.

16. The method according to claim 12 further comprising
administering a DNA molecule encoding PPAR γ or an inducer of a PPAR γ agonist to a mammal under conditions effective to cause transformation of
30 one or more cells in a target tissue, thereby promoting expression of PPAR γ or the inducer of a PPAR γ agonist in the target tissue.

17. A method of inhibiting thrombosis, the method comprising:
contacting mammalian platelets with an effective amount of PPAR γ , a
PPAR γ agonist, an RXR agonist, or a combination thereof, whereby said contacting
inhibits formation of a thrombosis by the mammalian platelets.
- 5 18. The method according to claim 17 wherein the mammalian
platelets are human platelets.
- 10 19. The method according to claim 18 wherein the PPAR γ is
human PPAR γ .
20. The method according to claim 17 wherein both the PPAR γ
agonist and the RXR agonist contact the mammalian platelet.
- 15 21. The method according to claim 17 wherein the PPAR γ agonist
is selected from the group consisting of cyclopentenone class prostaglandins,
lysophosphatidic acid or its derivatives, thiazolidinediones, glitazones, tyrosine-
derived agonists, indole-derived agonists, and combinations thereof.
- 20 22. The method according to claim 17 wherein the RXR agonist is
9-*cis*-retinoic acid, *trans*-retinoic acid, synthetic RXR agonists, and combinations
thereof.
- 25 23. The method according to claim 17 further comprising:
administering the PPAR γ agonist, the RXR agonist, or an inducer of a
PPAR γ agonist to a mammal in a manner that provides for said contacting.
- 30 24. The method according to claim 23 wherein the inducer of a
PPAR γ agonist is decorin or fragments thereof, or an enzyme that catalyzes formation
of prostaglandin D₂ precursor.
- 35 25. The method according to claim 23 wherein said administering
is carried out via topical application, intranasal instillation, inhalation, intravenous
injection, intra-arterial injection, intramuscular injection, application to a wound site,
application to a surgical site, intracavitary injection, by suppository, subcutaneously,

intradermally, transcutaneously, by nebulization, intraphurally, intraperitoneally, intraventricularly, intra-articularly, intra-aurally, intraocularly, or intraspinally.

26. The method according to claim 17 further comprising
5 administering a DNA molecule encoding PPAR γ or an inducer of a PPAR γ agonist to a mammal under conditions effective to cause transformation of one or more cells in a target tissue, thereby promoting expression of PPAR γ or the inducer of a PPAR γ agonist in the target tissue in a manner effective to cause said contacting.

10 27. A method of treating or preventing a thrombotic condition or disorder, the method comprising:
contacting mammalian platelets, in an individual exhibiting symptoms of or predisposed to a thrombotic condition or disorder, with an effective amount of
15 PPAR γ , a PPAR γ agonist, an RXR agonist, or a combination thereof, whereby said administering inhibits platelet activation to treat or prevent the thrombotic condition or disorder.

20 28. The method according to claim 27 wherein the mammalian platelets are human platelets and the individual is a human.

29. The method according to claim 28 wherein the PPAR γ is human PPAR γ .

25 30. The method according to claim 27 wherein both the PPAR γ agonist and the RXR agonist contact the mammalian platelet.

30 31. The method according to claim 27 wherein the PPAR γ agonist is selected from the group consisting of cyclopentenone class prostaglandins, lysophosphatidic acid or its derivatives, thiazolidinediones, glitazones, tyrosine-derived agonists, indole-derived agonists, and combinations thereof.

32. The method according to claim 27 wherein the RXR agonist is 9-*cis*-retinoic acid, *trans*-retinoic acid, synthetic RXR agonists, and combinations thereof.

5 33. The method according to claim 27 further comprising:
administering PPAR γ , the PPAR γ agonist, the RXR agonist, or an inducer of a PPAR γ agonist to the individual in a manner that provides for said contacting.

10 34. The method according to claim 33 wherein the inducer of a PPAR γ agonist is decorin or fragments thereof, or an enzyme that catalyzes formation of prostaglandin D₂ precursor.

15 35. The method according to claim 33 wherein said administering is carried out via topical application, intranasal instillation, inhalation, intravenous injection, intra-arterial injection, intramuscular injection, application to a wound site, application to a surgical site, intracavitary injection, by suppository, subcutaneously, intradermally, transcutaneously, by nebulization, intraplurally, intraperitoneally, intraventricularly, intra-articularly, intra-aurally, intraocularly, or intraspinally.

20 36. The method according to claim 27 further comprising administering a DNA molecule encoding PPAR γ or an inducer of a PPAR γ agonist to the individual under conditions effective to cause transformation of one or more cells in a target tissue, thereby promoting expression of PPAR γ or the
25 inducer of a PPAR γ agonist in the target tissue in a manner effective to cause said contacting.

30 37. The method according to claim 27 wherein the thrombotic condition or disorder is selected from the group consisting of stroke, venous or arterial thrombosis, disseminated intravascular coagulation, myocardial infarction, pulmonary thrombo-embolism, and pulmonary hypertension.

38. A method of improving the quality of a blood product, the method comprising:

providing PPAR γ , a PPAR γ agonist, an RXR agonist, an inducer of a PPAR γ agonist, or a combination thereof; and

5 introducing PPAR γ , the PPAR γ agonist, the RXR agonist, the inducer of a PPAR γ agonist, or the combination thereof, to a blood product, wherein the PPAR γ agonist, the RXR agonist, the inducer of a PPAR γ agonist, or the combination thereof inhibits clotting or activation of platelets in the blood product and thereby improves the quality thereof.

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39. The method according to claim 38 wherein the blood product is selected from the group consisting of whole blood, plasma, concentrated platelets, or a white blood cell product.

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40. The method according to claim 38 wherein the blood product is a mammalian blood product.

41. The method according to claim 40 wherein the mammalian blood product is a human blood product.

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42. The method according to claim 41 wherein the PPAR γ is human PPAR γ .

43. The method according to claim 38 wherein said introducing is
25 carried out prior to storage of the blood product.

44. The method according to claim 38 wherein the blood product is whole blood and said introducing comprises:

collecting whole blood from a patient into a receptacle comprising the
30 PPAR γ agonist.

45. The method according to claim 38 wherein the blood product is plasma or concentrated platelets and said introducing comprises:

collecting whole blood from a patient;

separating the plasma or concentrated platelets from the whole blood;

5 and

combining the PPAR γ agonist, the RXR agonist, the inducer of a PPAR γ agonist, or the combination thereof, with the plasma or concentrated platelets.

46. The method according to claim 38 wherein the blood product is plasma or concentrated platelets and said introducing comprises:

collecting whole blood from a patient;

combining the PPAR γ agonist, the RXR agonist, the inducer of a PPAR γ agonist, or the combination thereof, with the whole blood to form a treated mixture; and

15 separating the plasma or concentrated platelets from the treated mixture.

47. The method according to claim 38 wherein the PPAR γ agonist is selected from the group consisting of cyclopentenone class prostaglandins, thiazolidinediones, glitazones, tyrosine-derived agonists, indole-derived agonists, and combinations thereof.

48. The method according to claim 38 wherein the RXR agonist is selected from the group of 9-*cis*-retinoic acid, *trans*-retinoic acid, synthetic RXR agonists, and combinations thereof.

49. The method according to claim 38 wherein the inducer of a PPAR γ agonist is decorin or fragments thereof, or an enzyme that catalyzes formation of prostaglandin D₂ precursor.

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50. A stored blood product comprising:
a blood product that contains platelets and
an amount of PPAR γ , a PPAR γ agonist, an RXR agonist, an inducer of
a PPAR γ agonist, or a combination thereof that is effective to inhibit platelet
5 activation.

51. The stored blood product according to claim 50 further
comprising an anticoagulant.

10 52. The stored blood product according to claim 50 wherein the
PPAR γ agonist is selected from the group consisting of cyclopentenone class
prostaglandins, thiazolidinediones, glitazones, tyrosine-derived agonists, indole-
derived agonists, and combinations thereof.

15 53. The stored blood product according to claim 50 wherein the
RXR agonist is selected from the group of 9-*cis*-retinoic acid, *trans*-retinoic acid,
synthetic RXR agonists, and combinations thereof.

20 54. The stored blood product according to claim 50 wherein the
inducer of a PPAR γ agonist is decorin or fragments thereof, or an enzyme that
catalyzes formation of prostaglandin D₂ precursor.

25 55. The stored blood product according to claim 50 wherein the
blood product is whole blood, plasma, concentrated platelets, or a white blood cell
product.

56. A method of inhibiting platelet aggregation comprising:
contacting mammalian platelets with an effective amount of PPAR γ , a
PPAR γ agonist, an RXR agonist, or a combination thereof, whereby said contacting
30 inhibits aggregation of the mammalian platelets.

57. The method according to claim 56 wherein the mammalian
platelets are human platelets.

58. The method according to claim 57 wherein the PPAR γ is human PPAR γ .

59. The method according to claim 56 wherein both the PPAR γ agonist and the RXR agonist contact the mammalian platelet.

60. The method according to claim 56 wherein the PPAR γ agonist is selected from the group consisting of cyclopentenone class prostaglandins, lysophosphatidic acid or its derivatives, thiazolidinediones, glitazones, tyrosine-derived agonists, indole-derived agonists, and combinations thereof.

61. The method according to claim 56 wherein the RXR agonist is 9-*cis*-retinoic acid, *trans*-retinoic acid, synthetic RXR agonists, and combinations thereof.

62. The method according to claim 56 further comprising:
administering the PPAR γ agonist, the RXR agonist, or an inducer of a PPAR γ agonist to a mammal in a manner that provides for said contacting.

63. The method according to claim 62 wherein the inducer of a PPAR γ agonist is decorin or fragments thereof, or an enzyme that catalyzes formation of prostaglandin D₂ precursor.

64. The method according to claim 62 wherein said administering is carried out via topical application, intranasal instillation, inhalation, intravenous injection, intra-arterial injection, intramuscular injection, application to a wound site, application to a surgical site, intracavitary injection, by suppository, subcutaneously, intradermally, transcutaneously, by nebulization, intraplurally, intraperitoneally, intraventricularly, intra-articularly, intra-aurally, intraocularly, or intraspinally.

65. The method according to claim 56 further comprising
administering a DNA molecule encoding PPAR γ or an inducer of a PPAR γ agonist to a mammal under conditions effective to cause transformation of one or more cells in a target tissue, thereby promoting expression of PPAR γ or the

inducer of a PPAR γ agonist in the target tissue in a manner effective to cause said contacting.

5 66. A method of treating or preventing a CD40 ligand-mediated or thromboxane-mediated condition, the method comprising:

contacting platelets, in an individual exhibiting or predisposed to a CD40 ligand-mediated or thromboxane-mediated condition, with PPAR γ , a PPAR γ agonist, an RXR agonist, an inducer of a PPAR γ agonist, or a combination thereof, whereby said contacting inhibits the release of CD40 ligand and/or thromboxane by
10 platelets, thereby treating or preventing the CD40 ligand-mediated or thromboxane-mediated condition.

67. The method according to claim 66 wherein the PPAR γ is human PPAR γ .
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68. The method according to claim 66 wherein the PPAR γ agonist is selected from the group consisting of cyclopentenone class prostaglandins, lysophosphatidic acid or its derivatives, thiazolidinediones, glitazones, tyrosine-derived agonists, indole-derived agonists, and combinations thereof.
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69. The method according to claim 66 wherein the RXR agonist is selected from the group of 9-*cis*-retinoic acid, *trans*-retinoic acid, synthetic RXR agonists, and combinations thereof.

25 70. The method according to claim 66 wherein the inducer of a PPAR γ agonist is decorin or fragments thereof, or an enzyme that catalyzes formation of prostaglandin D₂ precursor.

71. The method according to claim 66 wherein the individual is
30 human.

72. The method according to claim 66 wherein the CD40 ligand-mediated or thromboxane-mediated condition is selected from the group consisting of diabetes, atherosclerosis, induced multiple sclerosis, asthma, venous or arterial
35 thrombosis, pulmonary fibrosis, systemic lupus erythematosus, renal fibrosis, hepatic

cirrhosis, cerebral gliosis, disseminated intravascular coagulation, myocardial infarction, pulmonary thrombo-embolism, and pulmonary hypertension.

73. The method according to claim 66 wherein said contacting is carried out by administering PPAR γ , the PPAR γ agonist, the RXR agonist, the inducer of a PPAR γ agonist, or the combination thereof to the individual in a manner effective to cause said contacting.

74. The method according to claim 73 wherein said administering is carried out via topical application, intranasal instillation, inhalation, intravenous injection, intra-arterial injection, intramuscular injection, application to a wound site, application to a surgical site, intracavitary injection, by suppository, subcutaneously, intradermally, transcutaneously, by nebulization, intraplurally, intraperitoneally, intraventricularly, intra-articularly, intra-aurally, intraocularly, or intraspinally.

75. The method according to claim 52 wherein said contacting is carried out by administering to the patient a DNA molecule encoding PPAR γ or the inducer of a PPAR γ agonist, said administering being carried out under conditions effective to cause transformation of one or more cells in a target tissue in a manner effective to cause said contacting.

76. The method according to claim 75 wherein the DNA molecule is in an expression vector or present as naked DNA.

77. The method according to claim 76 wherein the expression vector is an adenoviral vector or adenoviral associated vector

78. A method of assessing the activity of a compound as a PPAR γ agonist, the method comprising:

combining a compound with both platelets and a platelet activator;
determining the level of CD40 ligand or thromboxane released from the platelets; and

comparing the level of CD40 ligand or thromboxane released from the platelets to the level of CD40 ligand or thromboxane released from a standard,

wherein deviation from the standard, or absence thereof, indicates activity of the compound as a PPAR γ agonist.

5 79. The method according to claim 78 wherein said determining comprises:

 providing an antibody or binding portion thereof recognizing CD40 ligand or an antibody or binding portion thereof recognizing the thromboxane;

 contacting a sample from the combination with the antibody or binding portion thereof; and

10 detecting any reaction which indicates that CD40 ligand or thromboxane is present in the sample using an assay system.

 80. The method according to claim 79 wherein the assay system is selected from a group consisting of enzyme-linked immunoabsorbent
15 assay, radioimmunoassay, gel diffusion precipitin reaction assay, immunodiffusion assay, agglutination assay, fluorescent immunoassay, protein A immunoassay, immunoelectrophoresis assay, Western blot, immunodotblot, and immunoslotblot.

20 81. The method according to claim 78 wherein the standard comprises platelets in the absence of the activator, and said comparing assesses the absence of deviation between the combination and the standard.

 82. The method according to claim 78 wherein the standard
25 comprises platelets in the presence of the platelet activator, and a known PPAR γ agonist, and said comparing assesses the deviation between the combination and the standard.

 83. The method according to claim 78 wherein the platelet
30 activator is thrombin, epinephrine, collagen, or ADP.

84. A method of diagnosing a CD40 ligand-mediated condition comprising:

obtaining a patient sample and
determining the level of PPAR γ in the patient sample, wherein a
5 reduced PPAR γ level indicates the presence of a CD40 ligand-mediated condition.

85. The method according to claim 84 wherein said determining comprises:

providing an antibody or binding portion thereof recognizing
10 PPAR γ ;
contacting the sample with the antibody or binding portion thereof;
and
detecting any reaction which indicates that PPAR γ is present in the
sample using an assay system.

15 86. The method according to claim 85 wherein the assay system is selected from a group consisting of enzyme-linked immunoabsorbent assay, radioimmunoassay, gel diffusion precipitin reaction assay, immunodiffusion assay, agglutination assay, fluorescent immunoassay, protein A
20 immunoassay, immunoelectrophoresis assay, Western blot, immunodotblot, and immunoslotblot.

87. The method according to claim 84 wherein the CD40 ligand-mediated condition is selected from the group consisting of diabetes,
25 atherosclerosis, induced multiple sclerosis, asthma, venous or arterial thrombosis, pulmonary fibrosis, systemic lupus erythematosus, renal fibrosis, hepatic cirrhosis, cerebral gliosis, disseminated intravascular coagulation, myocardial infarction, pulmonary thrombo-embolism, and pulmonary hypertension.

30 88. The method according to claim 84 wherein the patient sample is selected from the group of blood, plasma, tissue washings, lung lavage, eye fluids, saliva, joint fluid, peritoneal fluid, stool, semen, gastric fluids, and thoracic fluids.

89. A method of assessing the efficacy of a PPAR γ agonist therapy, the method comprising:

obtaining a patient sample, the patient having been previously administered a PPAR γ agonist or an inducer of a PPAR γ agonist for treating a medical condition or disorder; and

determining the level of PPAR γ in the patient sample, wherein an elevated PPAR γ level, relative to a baseline PPAR γ level for the patient prior to said administration, indicates the efficacy of the PPAR γ agonist therapy.

90. The method according to claim 89 wherein said determining comprises:

providing an antibody or binding portion thereof recognizing PPAR γ ;

contacting the sample with the antibody or binding portion thereof;

and

detecting any reaction which indicates that PPAR γ is present in the sample using an assay system.

91. The method according to claim 90 wherein the assay system is selected from a group consisting of enzyme-linked immunoabsorbent assay, radioimmunoassay, gel diffusion precipitin reaction assay, immunodiffusion assay, agglutination assay, fluorescent immunoassay, protein A immunoassay, immunoelectrophoresis assay, Western blot, immunodotblot, and immunoslotblot.

92. A method of modifying megakaryocytes comprising: exposing a megakaryocyte to PPAR γ , a PPAR γ agonist, an RXR agonist, an inducer of a PPAR γ agonist, or a combination thereof, whereby said exposing phenotypically modifies the megakaryocyte to produce daughter platelets that minimize pro-inflammatory and/or pro-thrombotic responses by the platelets.

93. The method according to claim 92 wherein the PPAR γ is human PPAR γ .

94. The method according to claim 92 wherein the PPAR γ agonist is selected from the group consisting of cyclopentenone class prostaglandins, lysophosphatidic acid or its derivatives, thiazolidinediones, glitazones, tyrosine-
5 derived agonists, indole-derived agonists, and combinations thereof.

95. The method according to claim 92 wherein the RXR agonist is selected from the group of 9-*cis*-retinoic acid, *trans*-retinoic acid, synthetic RXR agonists, and combinations thereof.

10 96. The method according to claim 92 wherein the inducer of a PPAR γ agonist is decorin or fragments thereof, or an enzyme that catalyzes formation of prostaglandin D₂ precursor.

15 97. The method according to claim 92 wherein the megakaryocyte is a human megakaryocyte.

98. A method of treating or preventing a CD40 ligand-mediated or thromboxane-mediated condition, the method comprising:
20 treating a patient exhibiting or predisposed to a CD40 ligand-mediated condition with recombinant PPAR γ , whereby said treating inhibits the release of CD40 ligand and/or thromboxane by platelets, thereby treating or preventing the CD40 ligand-mediated or thromboxane-mediated condition.

25 99. The method according to claim 98 wherein the patient is human.

100. The method according to claim 98 wherein the CD40 ligand-mediated condition is selected from the group consisting of diabetes, atherosclerosis, induced multiple sclerosis, asthma, venous or arterial thrombosis,
30 pulmonary fibrosis, systemic lupus erythematosus, renal fibrosis, hepatic cirrhosis, cerebral gliosis, disseminated intravascular coagulation, myocardial infarction, pulmonary thrombo-embolism, and pulmonary hypertension.

101. The method according to claim 98 wherein said treating is carried out by administering the recombinant PPAR γ to the patient.

102. The method according to claim 101 wherein said administering
5 is carried out via topical application, intranasal instillation, inhalation, intravenous injection, intra-arterial injection, intramuscular injection, application to a wound site, application to a surgical site, intracavitary injection, by suppository, subcutaneously, intradermally, transcutaneously, by nebulization, intraplurally, intraperitoneally, intraventricularly, intra-articularly, intra-aurally, intraocularly, or intraspinally.

103. The method according to claim 98 wherein said treating is carried out by administering to the patient a DNA molecule encoding the recombinant PPAR γ , said administering being carried out under conditions effective to cause transformation of one or more cells in a target tissue, thereby promoting expression of
15 the PPAR γ in the target tissue.

104. The method according to claim 103 wherein the DNA molecule is in an expression vector or is naked DNA.

105. The method according to claim 103 wherein the expression
20 vector is an adenoviral vector or an adeno-associated viral vector.